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Unrecognised myocardial infarction and its relationship to outcome in critically ill patients with cardiovascular disease

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Author contributions: All authors were involved in the design of the study. ABD ran the study. SA, ASS, and AM performed the ECG analysis. ABD, NIL and TSW undertook the data analysis. All authors were involved in the interpretation of the data and the drafting of the manuscript.

Running title:

Myocardial infarction and outcome in cardiovascular ICU patients

Take-home message:

Around a quarter of patients with pre-existing cardiovascular disease experience myocardial infarction (MI) during ICU care, which is usually unrecognized in routine care and results predominantly from oxygen supply-demand imbalance (type 2 MI). Both myocardial injury (isolated troponin elevation) and MI are associated with worse short and long-term survival, and MI may be on the causal pathway between acute physiological derangement and mortality.

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Conflict of Interests: Dr Shah has received speaker fees from Abbott Diagnostics. Professor Mills has acted as a consultant for Abbott Diagnostics, Beckman-Coulter, Roche and Singulex who manufacture troponin assays, and has received research grants from Abbott Diagnostics.

Key words (4-6)

Critical care, Cardiovascular disease, Troponin, Myocardial Infarction, Cohort Study

Abstract:

Purpose

To establish the incidence of myocardial infarction (MI) in ICU patients with co-existing cardiovascular disease (CVD), and explore its association with long-term survival.

Methods:

In a multi-centre prospective cohort study in 11 UK ICUs we enrolled 273 critically ill patients with co-existing CVD. We measured troponin I (cTnI) with a high sensitivity assay for ten days; ECGs were done daily for five days and analysed by blinded cardiologists for dynamic changes. Data were combined to diagnose myocardial 'infarction', 'injury' or 'no injury' according to the third universal definition of MI. Patients were followed-up for six months. Regression and mediation analyses were used to explore relationships between acute physiological derangements, MI, and mortality.

Results:

cTnI was detected in all patients with a rise/fall pattern consistent with an acute hit. In 73% of patients this peaked on days 1-3 (median 114ng/l (1^{st},3^{rd} quartiles: 27, 393). Serial ECGs indicated 24.2% (n=66) of patients experienced MI, but >95% were unrecognized by clinical teams. Type 2 MI was the most likely aetiology in all cases. A further 46.1% (n=126) experienced injury (no ECG changes). Injury and MI were both associated with six month mortality (reference: no injury): OR injury 2.28 (95% CI 1.06-4.92, p=0.035), OR MI 2.70 (95% CI 1.11-6.55 p=0.028). Mediation analysis suggested MI partially mediated the relationship between acute physiological derangement and six month mortality (p=0.002) suggesting a possible causal association.

Conclusions:

Undiagnosed MI occurs in around a quarter of critically ill patients with co-existing CVD and is associated with lower long-term survival.

Around 20-30% of adult ICU admissions have pre-existing cardiovascular disease (CVD) [1, 2]. These patients are at risk of myocardial ischaemia during acute illness as a result of cardiovascular stress and reduced coronary oxygen delivery.

Diagnosing myocardial infarction (MI) is difficult in critically ill patients. The third universal definition of MI requires evidence of myocardial necrosis (elevation of myocardial injury biomarkers such as troponin), together with clinical symptoms, ischaemic ECG changes, regional wall motion abnormalities on echocardiography, or evidence of coronary thrombus [3]. MI is further categorized into Type 1 (plaque rupture) and Type 2 (oxygen supply-demand imbalance). Myocardial injury is isolated troponin elevation secondary to cardiac ischaemia. Troponin elevation is also known to result from other aetiologies including sepsis [4], pulmonary embolism [5], acute intracerebral pathology [6], and comorbidities such as COPD [7] and renal failure [8].In intensive care (ICU) patients, sedation and altered consciousness make application of the universal definition difficult.

In large studies of non-cardiac surgery myocardial injury is independently associated with worse outcomes [9, 10]. Furthermore, both type 2 MI and injury are associated with worse outcomes than type 1 MI [11-13]. Although some previous studies have measured troponins in ICU patient cohorts, no large studies have systematically used the universal definition to estimate myocardial injury and infarction events [2, 14, 15]. This is especially relevant to critically ill patients with pre-existing CVD, who are at greater risk due to established coronary artery lesions. It is also unclear whether myocardial injury or infarction are causally related to higher mortality, rather than simply associated with more severe illness. Understanding whether this association is, at least in part, causal has potential clinical relevance because, particularly for type 2 MI, it may justify interventions to optimise myocardial oxygen supply-demand balance such as anaemia correction or cardiovascular

manipulation. Current uncertainty is highlighted by the wide variation in clinical practice in response to troponin elevation between clinicians [16].

Our aim was to establish the incidence of myocardial injury and MI during ICU care according to the third universal definition in patients admitted with non-cardiac diagnoses but with known pre-existing CVD, and explore whether a causal relationship exists between acute physiological derangement, myocardial injury and MI, and six month mortality.

Methods

Study Design and setting

TROPICCAL (TROPonin I in Cardiovascular patients in CriticAL care, UKCRN 19253) was a prospective cohort study in 11 UK ICUs. Ethical approval was by Scotland A Research Ethics Committee, and Newcastle and North Tyneside Ethics Committees.

Participants

Inclusion criteria were critically ill adults with pre-existing CVD requiring admission to ICU. CVD was defined as any combination of: chronic cardiac disease, peripheral vascular disease, previous transient ischaemic attack or cerebrovascular accident, age ≥75yrs with diabetes or hypertension, or previous myocardial infarction or unstable angina (table E1). Patients with new ACS were excluded if this was the primary diagnosis. Patients or relatives were approached for consent depending on their capacity.

Data collection

We collected baseline demographic data and daily information for ten days regarding illness severity/organ support, and routine blood tests (see eSupplement). Daily troponin I (cTnI) was measured using the ARCHITECT STAT high-sensitive troponin I assay (Abbott

Diagnostics, Illinois, USA), a two-step immunoassay using chemiluminescent microparticle (CMIA) technology. The limit of detection was 1.2 ng/l, with an upper reference limit (99th centile) of 34 ng/L in men and 16 ng/L in women [17]. The co-efficient of variation is 10% at 6 ng/l [18] (see eSupplement). Clinicians were blinded to study cTnI data, but could order cardiac biomarkers at clinical discretion.

Daily ECGs were performed for up to five days post-admission. ECG interpretation was performed by cardiology research fellows, each with over ten years postgraduate experience, blinded to clinical information and cTnI results, for the following features: ST elevation/LBBB, ST depression, T wave inversion, new Q waves, RBBB (see eSupplement). Cardiologists also reported, as a binary outcome, whether serial ECGs indicated dynamic changes consistent with acute myocardial ischaemia.

Outcomes

Main outcomes were myocardial injury/infarction category, and 6 month mortality. Other outcomes were duration of mechanical ventilation, and length of ICU and hospital stay. MI was defined as TnI above the sex-specific upper reference limit with ≥20% rise and/or fall in cTnI concentrations, with evidence of dynamic ECG abnormalities suggesting ischaemia. Acute myocardial injury was defined as ≥20% rise and/or fall in cTnI, without ECG signs of ischaemia. Chronic myocardial injury was defined as a persistently elevated cTnI (<20% change) with no evidence of ischaemia. Patients in whom cTnI remained within the reference range and had no signs of ischaemia were defined as no injury [3]. Components of the SOFA score during the 24 hours preceding MI were used to qualitatively assess the likelihood of type 1 versus 2 aetiology.

Statistical analyses:

Myocardial injury and MI data: Data were analyzed using R (R Core Team v3.3.2, Vienna, Austria) [19]. Statistical significance was set at p=0.05. All tests were 2-sided. We presented continuous data as mean (95% CI), or median (IQR) if non-normally distributed. Binary data were presented as frequency (%). For univariate comparisons, we used the Student t test, ANOVA, Mann Whitney U, or Kruskal-Wallis test according to data distribution. Categorical data were compared using Fisher's exact test.

Relationship with mortality: We plotted unadjusted Kaplan Meier survival curves and compared group outcomes with the log rank test. As an exploratory analysis and to explore and illustrate the possible importance of baseline illness severity, we compared mortality outcomes for patients with higher versus lower acute physiological scores (APS, the acute physiological component for APACHE II scores) by dichotomizing the population using the median APS score. To further explore possible causal mechanisms between APS ("exposure"), MI ("mediator") and mortality at six months ("outcome") we undertook a mediation analysis [20] (see Figure E1). For this, we used a binomial ("probit") model using the mediation R package (see eSupplement for further explanation) [21]. We included variables with significant univariable association with mortality, and those considered clinically important.

We explored the association of myocardial injury category with six month mortality using multivariable logistic regression, including the same variables. APS was excluded from this model due to the potential for adjusting for a mediator.

Results

Between 15th February 2015 and 30th June 2016 we recruited 279 patients in 11 different UK National Health Service (NHS) regions (Consort diagram, figure E2; table E2). The prevalence of CVD among ICU admissions was 23.4% (table E2). Cohort characteristics are summarized in table 1. The majority of patients (91.4%) were on long-term medication for CVD (table E3).

Pattern of cTnI release

All patients had detectable cTnI during ICU stay. There was a wide range of cTnI at admission (median (1st, 3rd quartile, range) 36ng/l (13, 140, 1-45400ng/l)), and peak cTnI (median 114ng/l (27, 393; 3-58820ng/l) (figure 1). 64 (84.2%) women and 130 (66.0%) men had peak cTnI over the sex-specific diagnostic threshold for diagnosis of myocardial infarction or injury (overall total n=194 (71.1%), figure 1A). Peak cTnI for most patients (73%) occurred within 2-3 days of admission to ICU (figure 1B). Virtually all patients had a dynamic rise and fall pattern of cTnI release consistent with acute myocardial injury, which was apparent across all quartiles of peak cTnI (figure 2). Among the 37 (13%) of patients who died in ICU, 33 (89%) had dynamic rise and fall patterns before they died and four patients died on the day of peak cTnI. Patterns of TnI rise and fall were similar across severity of Acute Kidney Injury groups (figure E4, online supplement).

ECG abnormalities

There was excellent agreement between cardiologists regarding the presence/absence of acute myocardial ischaemia on serial ECGs (kappa 0.89, table E4). On admission to ICU 132 (47.3%) patients had a normal ECG (figure E3) of whom 19 (14.4%) had subsequent dynamic ECG changes consistent with acute myocardial ischaemia. Ninety one patients (32.6%) had an abnormal ECG on admission, of whom 44 (48.3%) had no subsequent

changes suggesting chronic abnormalities, but 47 (51.6%) had evolving changes consistent with acute myocardial ischaemia. In 24 patients (8.6%) no baseline ECG was available of whom 22 had no subsequent ECG abnormalities and two demonstrated dynamic changes consistent with acute myocardial ischaemia. Overall, 68 patients (24.4%) had dynamic abnormalities on serial ECG testing considered indicative of acute myocardial ischaemia.

Incidence of infarction and injury

Sixty eight patients fulfilled the universal definition for MI (24.4%, 95% CI 19.2% to 29.7%); 126 for acute injury (46.1%, 95% CI 40.1% to 52.3%); and 84 demonstrated no injury (30.7%, 95% CI 25.3% to 36.6%) (figure 3). The median peak cTnI for MI was significantly higher than for injury (infarction 375ng/l vs injury 138ng/l, $p<0.001$). Only 4.3% (n=12) of patients were diagnosed with MI by the clinical teams, of whom only three fulfilled the universal definition of MI. Twenty four percent (N=65) of the patients therefore experienced clinically undiagnosed MI according to the universal definition.

Physiological data relevant to coronary oxygen supply-demand imbalance during the 24 hours preceding the peak TnI for each patient suggested that type 2 MI was the most likely mechanism in all patients (table E5). Specifically, all patients (n=68) were receiving medium or high dose vasoactive drugs (57% (n=39) high dose) but, despite this, 37% (n=25) had a lowest MAP ≤60mmHg. Sixty percent (n=41) had a highest lactate ≥2mmol/l and 40% (n=27) had a lowest haemoglobin ≤90g/l.

Mortality, duration of mechanical ventilation, and length of stay

Survival curves according to injury category are shown in figure 4. Patients experiencing infarction and injury had lower survival over six months than patients with no injury (P=0.003; Figure 4A; Table E6), but without statistically significant differences between the injury and infarction groups. When dichotomised by median APS (median=13), patterns of

survival were different between the injury/infarction groups. For APS>13 (greater physiological derangement) there were differences across the groups (P=0.042), but injury and MI groups had similar survival curves. However, for APS≤13 (less physiological derangement), differences between groups were more marked (p=0.005) and patients experiencing MI had higher mortality than those in both injury and no injury groups (Figure 4B, 4C). The interaction between APS and MI was significant (p=0.035) suggesting that the relationship between injury/infarction category and mortality may differ according to the early severity of physiological derangement. TnI release was lower in the Injury patients versus the MI patients for the lower APS sub-group, but substantially higher in the Injury patient (and similar to MI patients) in the higher APS sub-group (figure E5).

Length of ICU and hospital stay was similar across categories (table E6), but patients experiencing MI had longer median (1^{st}, 3^{rd} quartile; range) duration of MV than patients with injury, or no injury (MI 4 days (2, 7; 0-39); injury 2 days (0, 5; 0-31); no injury (1 day (0, 4; 0-33); P=0.001 infarction versus injury).

Independent and potential causal relationship between injury, MI, and mortality

The mediation model suggested that APS ("Exposure", Estimate 0.114, p=0.0005) and MI ("Mediator", Estimate 2.50, p=0.006) were significantly associated with mortality at six months ("Outcome"). Mediation analysis estimated that 63.0% of the effect on six month mortality from APS lay on the direct route (Average Direct Effect: b=0.006, 95% CI 0.003 to 0.010, p=0.001), but 37.0% of the effect was mediated through MI (Average Causal Mediation Effect: b=0.0038, 95% CI 0.001 to 0.007, p=<0.001, Figure E6). This confirmed the expected significant relationship between APS and mortality, but suggested that the occurrence of an MI was on a causal pathway for part of this relationship.

There was a strong univariable association between six month mortality and injury/infarction category (Ref: no injury, Injury OR 2.96 (95% CI 1.45, 6.03), MI OR 3.35 (95% CI 1.51, 7.43). This persisted after adjustment for confounders: OR injury 2.28 (95% CI 1.06 to 4.92), Infarction 2.70 (95% CI 1.11 to 6.55) (table E8).

Discussion

We found cTnI was detectable in all critically ill patients admitted to ICUs with pre-existing CVD, and consistently demonstrated a rise and fall pattern in keeping with an 'acute hit' mechanism of injury. Detailed prospective classification of myocardial injury and infarction indicated an incidence of MI of 24.2%, with >95% undiagnosed by clinical teams. The physiological status of all patients with MI suggested potential coronary supply/demand imbalance, and likely type 2 MI rather than plaque ruptures or other coronary occlusive events. Both myocardial injury and infarction were associated with higher six month mortality, which in adjusted logistic regression suggested an independent association. Exploratory analyses of sub-groups with greater or lesser acute physiological derangement suggested the association between MI and mortality may be strongest among patients with less acute physiological derangement. Importantly, a mediation analysis exploring whether MI mediates part of the relationship between APS and mortality suggested it did contribute on the causal pathway.

The prevalence of CVD was 23.4% in this study, which is similar to previous studies [1, 2] and highlights the importance of understanding whether ICU care should be modified for this population. Although peak cTnI concentrations varied widely, in virtually all patients there was a characteristic rise/fall pattern suggesting an acute mechanism of injury and the patterns cTnI were broadly similar to the log linear decrease seen post primary angioplasty for ST

elevation MI. This suggests an acute 'hit' within the first 2-3 days of admission in most patients [22]. Of relevance, patterns were similar across all grades of renal injury.

The blinded systematic approach by cardiologists used to discriminate injury from MI has been shown to result in higher diagnostic agreement compared with non-cardiologist interpretation [23], and demonstrated fair to good agreement for ST elevation and ST depression. The poorer reliability of T-wave inversion is also consistent with previous literature suggesting this is a less valid measure of ischaemia [24-26]. We used dynamic ischaemia using all ECGs to define MI, which had high reliability. This was important because a third of patients had abnormal baseline ECGs, of whom only one half experienced dynamic changes. Although the absence of clinical symptoms made temporal relationships between ECG changes and troponin release difficult to interpret, we observed closely concurrent changes in patients within the first 2-3 days in the majority of patients, suggesting we achieved high diagnostic accuracy for injury and MI. This was in contrast with non-systematic approaches by clinicians which resulted in very low identification of MI. Only a quarter of patients diagnosed clinically with MI fulfilled the universal definition.

Both injury and MI were significantly associated with six month mortality, which is consistent with published literature for troponin in both perioperative and critical care practice where elevated troponin levels are associated with greater mortality irrespective of the etiology of release [2, 14, 27-30]. Only two previous ICU studies analyzed both troponin and ECG data concurrently; both were in general ICU populations rather than restricted to patients with co-existing CVD [2, 15]. Lim et al found 50% of 103 patients had an elevated TnT (threshold of 40ng/l) [15], of whom half were judged to have had an MI, and more than 30% of these a Type 2 MI. However, classification for Type 2 MI required no history of coronary artery disease or risk factors. Ostermann et al found the majority of critically ill patients (84%, total study n=144) had a TnT rise (threshold 15ng/l); 41% met criteria for MI,

of whom only 20% were recognized clinically. In both studies patients with TnT increase had higher mortality. Our multicentre study restricted to patients with pre-existing CVD reports the most detailed evaluation to date, and confirms high rates of unrecognized MI in this population (around a quarter of patients).

To address the key question of whether myocardial injury or infarction have any causal association with mortality, we used mediation analysis. Our analysis confirmed the expected direct effect of acute physiological derangement on mortality, but suggested that around a third of this effect may be mediated through MI events. Although we cannot be sure of the mechanism of MI, all patients who were diagnosed with MI were on high dose vasopressors from a pathophysiological perspective this is consistent with oxygen supply-demand imbalance (Type 2 MI). However, inflammation in the critically ill patient may also be associated with greater risk of plaque rupture and type 1 MI. A potentially causal relationship between MI and mortality supports the hypothesis that interventions to optimize myocardial oxygen/supply demand balance might improve outcomes in patients with pre-existing CVD, and future randomized trials are likely to be the best way to address this. Our exploratory sub-group analysis suggested the association between MI and mortality may interact with acute physiological derangement, with greater effects from MI observed in less deranged patients. This relationship appeared different for myocardial injury alone. This hypothesis-generating observation has potential biological plausibility, because mortality attributable to new MI may be proportionately greater in patients with less severe illness.

Strengths of our study include the use of a highly sensitive cTnI assay across a range of ICUs, and inclusion of a range of pre-existing CVD categories suggesting generalisability. We also had few missing data and complete patient follow up. Our study has several weaknesses. Patients may have had further episodes of injury or MI later in their hospital stay, and we only captured events during the first 5 days in ICU. We recorded admission cardiac

medications, but not whether these were continued or stopped during the ICU admission as this was not the aim of the study. Although our study is the largest to date, with a high event rate, the power of our analyses was restricted by sample size and could be subject to both type I and II error. Due to sample size we dichotomised on median APS score rather than reporting in tertiles or quartiles. The mediation analysis allowed novel exploration of possible causal mechanisms, but a randomized trial would be needed to know if strategies aimed at manipulating physiological variables can prevent MI and improve outcomes. Candidate components of an intervention to decrease coronary oxygen-supply imbalance include a more liberal transfusion practice, and it is notable that nadir haemoglobin was also independently associated with mortality in our analysis. Recent meta-analyses suggest that liberal transfusion strategies may decrease MI rates in both patients with CVD [31] and without known CVD [32]. The TRICS III trial suggested heterogeneity within the cardiac surgery population [33], highlighting further that personalised approaches to transfusion may be context specific. Other potential interventions include continuation or initiation of cardiac medications. There is substantial clinical uncertainty and practice variation regarding primary and secondary interventions for injury and MI in ICU patients [13, 16]. Our data support the need for further research to clarify best practice in patients at high risk of MI, such as those with pre-existing CVD.

Conclusion

In conclusion, we have demonstrated that around a quarter of patients with pre-existing CVD experience MI during ICU care, which is usually unrecognised in routine care. Both myocardial injury and infarction are associated with worse short and long-term survival, andMI may be on the causal pathway between acute physiological derangement and mortality. These data support future research to explore whether ICU interventions to reduce MI in patients with pre-existing CVD can improve outcomes.

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Figure legends:

Figure 1. A) Peak cTnI concentration for each patient (n=273) on a logarithmic scale (blue dots are men, red dots are women). Horizontal lines represent the sex-specific upper reference limits for men and women with 130/197 (66.0%) men and 64/76 (84.2%) women respectively above this threshold. B) Histogram showing the day of peak cTnI concentration for all patients (day 1 is the first day of ICU admission).

Figure 2: Change in cTnI concentrations centred around the peak concentration. Each coloured line represents a separate patient. The black line represents the "average" patient (the smoothed conditional mean with 95% confidence intervals). A) cTnI concentrations as a percentage of the peak concentration in all patients. B) cTnI concentrations stratified into quartiles to display the rise and fall pattern across the range of peak cTnI concentrations (Q1 cTnI <25 ng/l, Q2 cTnI 25-107 ng/l, Q3 cTnI 107-380 ng/l, Q4 cTnI >380ng/l [Q4 on logarithmic scale]).

Figure 3: n=273. Dynamics of peak cTnI by No injury (cTnI<threshold, n=84, 30.7%); Injury (cTnI>threshold, no dynamic ECG ischaemia, n=126, 46.1%); Infarction (cTnI elevation + dynamic ECG ischaemia, n=66, 24.2%). cTnI is plotted on log10 scale. Box plots represent median and IQR. Horizontal dotted line at sex specific thresholds cTnI=16 & 34ng/l.

Figure 4: Kaplan Meier survival plots, stratified by group (red, no injury; green, acute myocardial injury; blue, myocardial infarction). A) All patients, log rank test Chi^2= 11.8 (df=2), p=0.003. B) Patients with Acute Physiological Score >13 (median population value), log rank test Chi^2=6.4 (df=2), p=0.042. C) Patients with Acute Physiological Score ≤13, log rank test Chi^2=10.5 (df=2) p=0.005.

Table 1: Baseline Characteristics for whole cohort. N=279. Patients can appear in more than one CVD category and more than one Chronic cardiac disease category.

Variable	n or mean/median	% or SD or IQR
	279	
Age mean(SD)	72.3	10.9
Male sex n(%)	200	71.7
Chronic cardiovascular disease eligibility diagnosis n(%)		
Acute Coronary Syndrome	22	7.9
Cerebrovascular accident/Transient ischaemic attack	42	15.1
Peripheral Vascular Disease	55	19.7
≥75 with Diabetes Mellitus/Hypertension	90	32.5
Chronic cardiac disease	174	62.4
Coronary artery disease	67	38.5
Congestive cardiac failure	27	15.5
Valvular disease	26	14.9
Arrhythmia	65	37.4
Hypertensive heart disease	58	33.3
Hypercholesterolemic heart disease	13	7.5
ICU admission diagnosis system n(%)		
Respiratory	65	23.3
Cardiovascular	64	22.9
Gastrointestinal	84	30.1
Neurological	12	4.3
Genito-urinary	31	11.1
Other	22	7.9
Comorbidity assessment		
Apache: 0	233	83.5
1	36	12.9
≥2	10	3.6
Functional comorbidity index score med(IQR)	2	1,3
Type of admission n(%)		
Elective Surgical	56	20.1
Emergency Surgical	81	29
Non-operative	142	50.9
Severity of Illness in first 24h		
APACHE II score	18	15,23
SOFA score	7	5,10
Vasopressors n(%)	104	37.3
Mechanical Ventilation n(%)	134	48.2
Renal Replacement Therapy n(%)	8	2.9
pre ICU Length of Stay (d) med(IQR)	1	0,2
Haemoglobin at admission g/l med (IQR)	111	93,125
Troponin at admission ng/l med (min, IQR, max)	26	1, 7 ,56, 2157

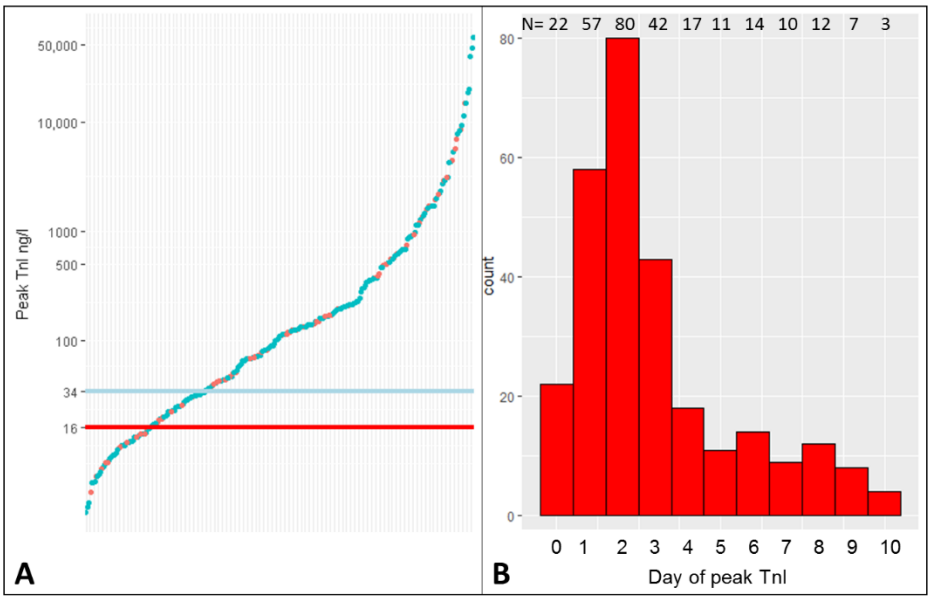

Figure 1

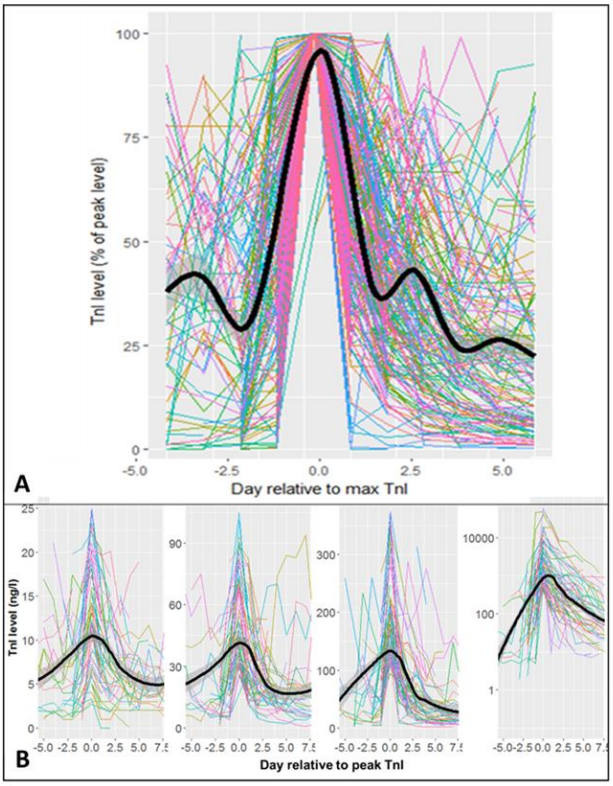

Figure 2

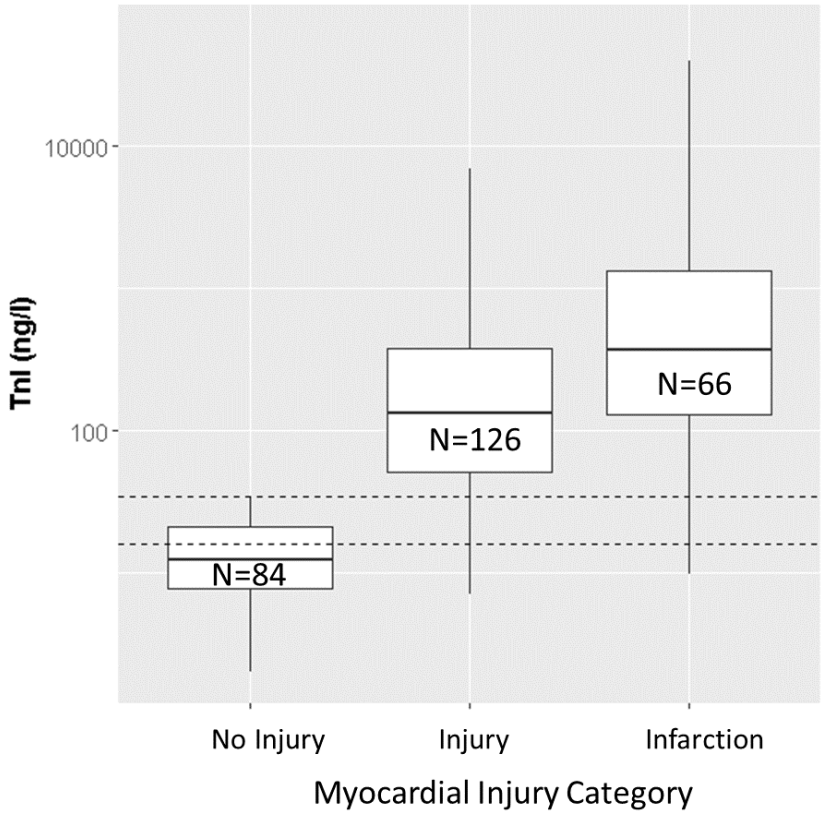

Figure 3

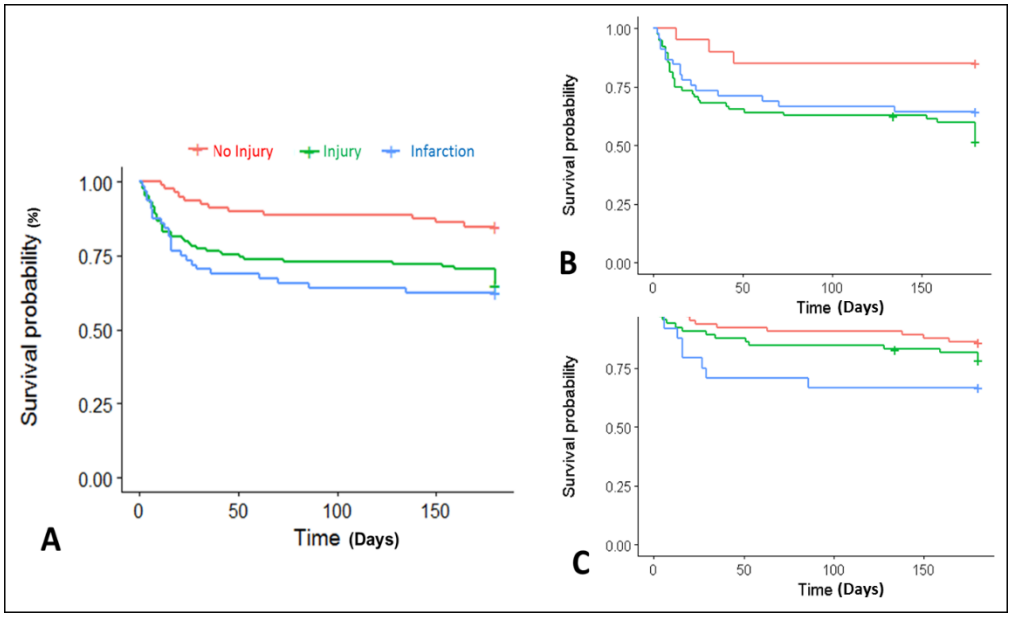

Figure 4